REMARKS

Status of the Claims.

Claims 1-12, 14-17, and 33 are pending with entry of this amendment, claim 33 being added herein. Claims 1, 6, 9, and 11 are amended herein. The amendments conform the claims to the preamble of claim 1 and clarify that the method relates to detecting a breast cancer marker. Support for the amendments are found at least a page 20, lines 6-9. Support for new claim 33 is found at least at page 26, lines 12-14. Therefore, these amendments introduce no new matter.

Information Disclosure Statement.

Applicants note with appreciation the Examiner's thorough consideration of the reference cited in the Information Disclosure Statement (Form 1449) submitted on October 22, 2007.

35 U.S.C. § 112, Second Paragraph.

Claims 1, 9-12, and 15-17 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because "they do no recite how CYP24 protein is measured and what assays are required in quantization of the said protein." Office Action, page 5. This rejection is respectfully traversed.

In explaining the rejection, the Examiner states that the "method steps should at least include reagents necessary for the assay, a detection step in which the reaction products are quantitated or visualized and a correlation step describing how the results of the assay allows [*sic*] the determination of for example, the detection of a disease." *Id.* Applicants respectfully point out that the only pending independent claim, claim 1, recites "detecting the level of CYP24 nucleic acid or CYP24 protein." Therefore, claim 1 does, in fact, recite a detecting step. Claim 1 also recites "comparing said level of CYP24 nucleic acid or CYP24 protein with a level of CYP24 nucleic acid or CYP24 protein in a control sample taken from a normal, cancer-free tissue; wherein an increased level of CYP24 nucleic acid or CYP24 protein in said biological sample compared to the level of CYP24 nucleic acid or CYP24 protein in said control sample indicates the presence of, or a predisposition to, breast cancer in said human." Accordingly, claim 1 also recites a correlation step describing how the result of the assay indicates the presence of, or a predisposition for, disease. This leaves the recitation of "reagents

necessary for the assay" as the only possible allegedly required component of the claimed method that is missing from the claims. Applicant respectfully submit that this component is not required and that including such a component in the claims would actually render the claims less clear.

The Examiner believes that the claims should set forth any reagents necessary for measuring CYP24 protein level. However, the means for detecting CYP24 protein level are non-critical. Applicants' specification sets forth 14 different exemplary analytic biochemical and immunochemical methods for detecting CYP24 protein level. Applicants' specification, page 25, lines 19-27. In addition, Applicants' specification indicates that methods for measuring CYP24 activity are well known and describes two such exemplary methods. *Id.*, page 28, 14-23. If Applicants were to attempt to incorporate reagents for each of these methods into the claim, the claim would be less clear than it is now. Moreover, doing this would not result in adequate claim coverage for Applicants' contribution to the art. This contribution relates the discovery that elevated CYP24 is correlated with breast cancer. It is this correlation, and the claimed methods for making use of this correlation that are important, not how CYP24 nucleic acid or protein is measured.

It is well-settled that one "does not look to the claims to find out how to practice the inventions they define, but, rather, to the specification." *In re Rainer, Redding, Hitov, Sloan, and Stewart,* 134 U.S.P.Q. 343,346 (C.C.P.A. 1962). Applicants submit that one of skill in the art knows when he/she is "detecting the level of CYP24 nucleic acid or CYP24 protein," and when he/she is not. Accordingly, the metes and bounds of the pending claims are clear without reciting "reagents necessary for the assay." Withdrawal of the § 112 indefiniteness rejection of claims 1, 9-12, and 15-17 is therefore respectfully requested.

New claim 33 recites the level of CYP24 protein is measured by immunoassay using at least one antibody that specifically binds to CYP24 protein. Because claim 33 recites a necessary reagent for a CYP24 immunoassay, Applicants submit that new claim 33 is free of this rejection.

Claim 1 was deemed vague and indefinite because the last line of the claim recited "cancer," whereas the preamble recited "breast cancer." Office Action, page 5. Also, dependent claims 6, 9, and 11 recited "cancer." *Id.* All of these occurrences of the term "cancer" have been amended to "breast cancer." Withdrawal of this rejection is respectfully requested.

35 U.S.C. § 112, First Paragraph.

Written Description

Claims 1-12 and 14-17 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. This rejection is respectfully traversed.

In explaining the rejection, the Examiner stated:

> While the Examiner notes the Google search of *CYP24* gene provide enumerable "hits" and the gene is well-established in the art, the crux of the issue is not that the gene is not well characterized and not established in the art, but how Applicants have defined the CYP24 gene in their specification Information provided in the specification sets forth "*CYP24* gene" is a DNA sequence that encodes a 24-hydroxylase enzyme . . . The term gene can refer to a mutated copy of the gene, or a fragment of the gene", see page 7, lines 10-12.

Office Action, page 3. Applicants appreciate this clarification. Applicants have amended claim 1 to make express that which is inherent in the claims and specification, namely that the "CYP24 nucleic acid or CYP24 protein is a nucleic acid or protein encoded by the **endogenous** vitamin D 24 hydroxylase (*CYP24*) gene." Moreover, since the claim relates to assaying human samples, the claim relates to the endogenous human gene. The specification cites GenBank Accession No. U60669, which provides the sequence of the "Human 1 alpha, 25-dihydroxyvitamin D3 24-hydroxylase (CYP24) gene," as it is identified in this GenBank record, which includes a sequence that was entered on February 8, 2002, almost 2 months before the priority date of the application. The claim thus requires the detection of protein or nucleic acid corresponding to a known endogenous human gene in a human sample. Applicants were clearly in possession of this invention at the time the application was filed, especially in view of the examples illustrating the detection of DNA, RNA, and protein corresponding to this gene.

The definition cited by the Examiner does not, in any way, detract from the fact that the endogenous vitamin D 24 hydroxylase (CYP24) gene is more than adequately described. Applicants note that the definition states that the "term gene **can** refer to a mutated copy of the gene, or a fragment of the gene." The word "can," implies "need not." Accordingly, in some embodiments, the term "gene" can refer to a mutated copy of the gene or a fragment, but in other embodiments, the term "gene" refers to the wildtype, full-length CYP24 gene.

The method of claim 1 requires, simply, the detection of nucleic acid transcribed from, or protein encoded by, the CYP24 gene in the sample. In other words, the measurement of the CYP24 protein or nucleic acid that is present. The specification describes an actual reduction to practice of this method in Example 1 and provides illustrative protocols in Examples 2 and 3. Therefore, there can be no question but that the claimed method is adequately described in the specification. Withdrawal of the § 112 rejection for lack of written description is respectfully requested.

Enablement

Claims 1-12 and 14-17 were rejected under 35 U.S.C. §112, first paragraph, "because the specification, while being enabling for a method of detecting *CYP24* mRNA is human breast tumor *in vitro* specimens treated with 1,25-dihydroxyvitamin D-3 comprising RT-PCR, [the specification] does not reasonably provide enablement for a method of detecting a predisposition to any cancer comprising detecting the level of *CYP24* nucleic acid or *CYP24* protein in a biological sample." Office Action, pages 3-4. This rejection is respectfully traversed.

In response to the statement above that the specification does not enable "detecting a predisposition to **any** cancer," Applicants respectfully point out that the claims unambiguously relate to "detecting a predisposition to breast cancer." This leaves the issue of enablement for "detecting the level of *CYP24* nucleic acid or *CYP24* protein in a biological sample." However, the Examiner states that she "does not doubt the ability of one of ordinary skill in the art to detect *CYP24* mRNA and protein levels." *Id.* Presumably, the Examiner also does not doubt the ability of one of skill to detect *CYP24* DNA, especially in view of Example 1, which discusses the use of comparative genomic hybridization (CGH), specifically array CGH, to detect amplification (DNA copy number increases). See Applicants' specification, page 52, line 23 – page 53, line 10.

The Examiner's issue appears to be that "the claims read on prevention and forecasting whether or not a person will develop cancer." Office Action, page 4. First, the previous language of the preamble of claim 1, "detecting a predisposition to breast cancer" does not require prevention of cancer. Claim 1 as amended recites "detecting a breast cancer marker." Therefore, to the extent that the rejection is based on a failure of the specification to enable cancer prevention, the rejection is improper. To enable the pending claim, Applicants' specification need only enable the detection of CYP24 nucleic acid and protein.

As those of skill in the art readily appreciate, a marker of disease typically indicates that disease is present or that the subject having the marker is predisposed to develop the disease. Markers are useful even though many markers do not definitively identify disease presence or predisposition. Individual markers may be combined with other parameters to arrive at a differential diagnosis.

In the Office Action, the Examiner notes that the Examples include data from established breast cancer cell lines. *Id.* However, in Example 1, Applicants demonstrated by array CGH that "expression of *CYP24* and *VDR* was detected in two breast cancer tumors S21 and S59." Applicants' specification, page 53, lines 20-21. Figure 3 shows that the expression levels in these tumors are as high as, or higher than, that in established breast cancer cell lines treated with 1,25-dihydroxyvitamin D-3. These data confirm the association between *CYP24* and breast cancer, supporting the use of CYP24 as a breast cancer marker in humans.

Accordingly, Applicants submit that the specification fully enables the pending claims. Withdrawal of the § 112 rejection for lack of enablement is therefore respectfully requested.

Conclusion.

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. Should the Examiner seek to maintain the rejections, Applicants request a telephone interview with the Examiner and the Examiner's supervisor.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 267-4160.

Any required fees accompany this response; if the amount of such fees is incorrect, please charge any required fees, or credit any overpayments, to Deposit Account No. 500388 (Order No. UCOTP089US).

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Respectfully submitted,

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